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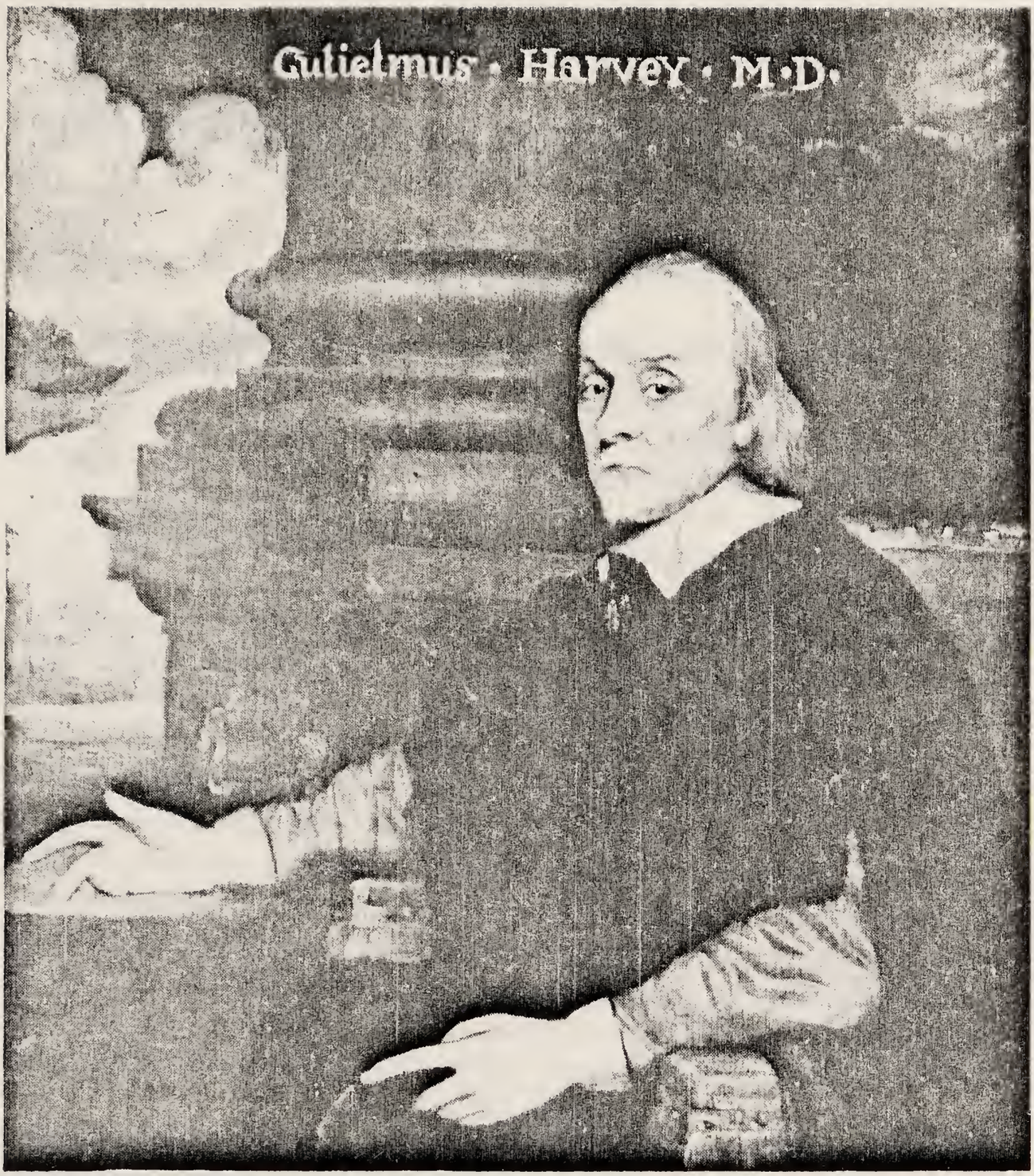

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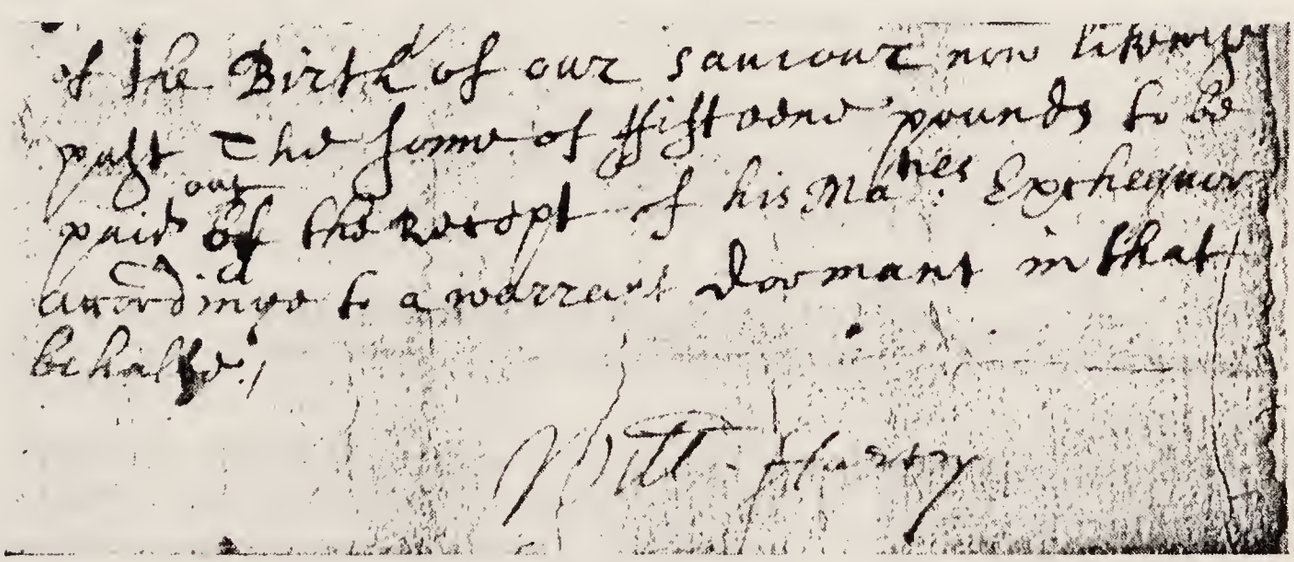

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THE SYMPATHETIC CONTROL OF THE MOTION OF THE BLOOD IN ITS VESSELS

By W. D. M. Paton

No experimental worker can feel much at ease speaking in the shadow of William Harvey. At the beginning of his anatomy lecture notes he instructs us to 'cut up as much as may be in the presence of your audience', and 'not to speak anything which without the carcass may be delivered or read at home'. It is obvious from the whole of his writing that experiment and demonstration mattered more to him than talk. But his advice ends by recommending that the lectures should serve 'in their three courses, according to the glass, first the lower parts of the abdomen, nasty, yet recompensed by admirable variety: second the parlour (i.e. the thorax); third the divine banquet of the brain'[3]. So that it is appropriate that we should in this session turn towards the nervous factors which control cardiovascular activity. It seems that Harvey himself did not, and indeed could not, attack this problem with the knowledge of physics and physiology then available. That he was aware of the scope of such work is obvious from a passage in his second letter to John Riolan Jun., where, after pointing out the ways in which the circulation may be involved in the responses to heat, cold, haemorrhage, fever, anger, lust and fear, he adds: 'Such a flood of light and truth breaks in upon me here; occasion offers of so many problems, of resolving so many doubts, of discovering the causes of so many slighter and more serious diseases, and of suggesting remedies for their cure, that the subject seems almost to demand a separate treatise'[4].

Since his day a vast mass of information has accumulated about the nervous pathways connecting the brain to the blood vessels and to the heart, about the afferent stimuli which may elicit reactions from the central nervous system, and about the physiological processes which may be mediated by these various pathways. We know indeed that we have to take into account not only nervous influences but also local effects of muscular movement, metabolites released by active tissue, the influence of circulating hormones, and probably also vasodilator materials such as bradykinin formed locally in the tissues. But in this paper I only want to take up a few

selected points in one part of the field, that of the autonomic sympathetic nervous system, with the particular intention of seeing how far our view of it has developed as a result of work in recent years.

RECENT GANGLION BLOCKING AGENTS

First, however, I ought to outline the existing position about ganglion blocking agents themselves, since these are amongst the commonest drugs now used for interfering with the nervous control of the circulation.

Tetraethylammonium, the oldest of the pure blocking agents, has now almost come to the end of its experimental usefulness, although it is still of great interest. Its defects are those of brevity of action and of side effects. Its action is so short as to make it difficult to reach an equilibrium state. Its side actions (including paraesthesiae which may be quite unpleasant, the stimulation of production of adrenaline in the blood, a curare-like effect which is produced by doses not much bigger than ganglion blocking doses, and certain curious reflex effects) muddy the pool of clinical interpretation so much that it is difficult to be certain that effects observed are certainly due to ganglion block. A great deal more satisfactory is hexamethonium which is highly specific, and exerts, in doses used in clinical practice, virtually only one action, ganglion paralysis. Some differences have been described between different preparations which rested simply on what sort of hexamethonium was used, whether iodide, bromide, tartrate or chloride. Its defects clinically, of course, are that it is poorly, and worse still irregularly, absorbed by mouth, and that for general clinical practice its duration of action is rather short. For investigation, however, there is still a great deal to be said for it, since it is quick in action, and has a reasonable duration of action, but not so long that recovery is delayed. Clinically, pentolinium, closely related structurally, is better, and probably in some cases still the drug of choice. Its advantages seem to rest in being more potent (so that a smaller total dose needs to be given), and in the slower onset of effect coupled with a prolonged action, which diminishes the number of doses per day, and yields a smoother control of the blood pressure. Apart from these pharmacodynamic features, pentolinium is exactly the same as hexamethonium.

Recently some new agents have appeared. Chlorisondamine (Ecolid, CIBA) seems in general to be like hexamethonium and pentolinium; a pure ganglion-blocking agent, but with a greatly prolonged duration of action so that its effects may last for as long as

a day and a half, against the six or eight hours of pentolinium and the three or four hours of hexamethonium. But with the other new product, mecamylamine, a new point arises. The earlier compounds I have mentioned are quaternary salts; this means that they can only exist as ions bearing a positive charge. As a result, since they have to carry this positive charge through any cell membrane they attempt to pass, penetration through cellular barriers is limited. From this property springs (for hexamethonium, pentolinium and chlorisondamine) bad absorption by mouth, the predominantly extracellular existence which they lead, their failure to be metabolized, their lack of central actions, and their excretion by the kidney largely by simple glomerular filtration. But mecamylamine is not quaternary but a secondary amine. It is, in fact, a fairly strong base and in solution most of it is in the charged form; but a small fraction, probably less than 1 per cent, is uncharged (that is, un-ionized), and hence is able to diffuse through membranes relatively easily. One imagines that to this is due to the way it can be absorbed by mouth, and the manner in which it is distributed throughout all the tissues in the body and indeed concentrated by some of them. But a third feature is of particular interest, that of its urinary excretion. We now know that if urine is acidified mecamylamine excretion is promoted; if urine is made alkaline it is depressed. One can relate this (although this does not account for the whole effect) to the effect of urinary *p*H on the ionization of the drug in the tubules. If the urine in the tubles is very alkaline, then more of the drug will be in the uncharged form and hence can be reabsorbed easily; on the other hand, when the urine is acid the drug will be much more ionized and less will be available in the form which passes through the tubules easily, and hence reabsorption should be depressed. But it seems likely that the handling of mecamylamine in ionic form may also be important. A recent brief (and undetailed) note[5] claims that mecamylamine and potassium can behave as though they were competing for excretion by the renal tubules. It is known that other strong bases are actively handled by the kidneys, and a fascinating prospect opens up of such bases influencing, and being influenced by, common cations of the body.

Now, from what one has said about mecamylamine it is obvious that two other possibilities of action may be important. The first is that if these ganglion blocking agents possess any central action, then one would be more likely to see it with mecamylamine than with the other drugs, simply because it is more likely to get through to the

central nervous tissue. The second is that by the same token it will be able to penetrate cells and there either be metabolized or interfere with the metabolism of the cells or even exert some other action. It is interesting in fact that there are a number of oddities about the pharmacology of mecamylamine. Dr. Zaimis has found it to possess properties unlike those of other typical ganglion blocking agents. Recently I have started testing its effect on acetylcholine production, and found that it can reduce the output of acetylcholine from a piece of eserinized intestine quite substantially, in a way that hexamethonium does not do. How far its effects in man are other than by ganglion block remains to be determined. For the moment, perhaps one must treat it as a ganglion blocking agent, with a wary eye open for the unexpected.

THE INTERPRETATION OF AUTONOMIC EFFECTS

There is a second preliminary point I should stress: that autonomic effects are not always simple. For instance, the removal of sympathetic activity does not invariably lead to reduction of function of some part of the body. A particularly striking incidence of this, not a cardiovascular one, is the effect of a ganglion blocking agent on intestinal motility in an anaesthetized cat, which Dr. Zaimis and I reported[8]. Here, as Bayliss and Starling showed many years ago, the intestine is held quiet by the activity of the splanchnic nerves. If this splanchnic action is abolished, either by section of the nerves or by paralysis of the ganglia from which they arise, then the intestine leaves its quiet, rather flaccid state and becomes the seat of violent incoordinate contractions. The probability of a cardiovascular analogy of this is small, but one can certainly think of some conditions, such as persistent excitation of the vagus, in which the onset of ganglion block might actually produce an increased activity of the heart and a rise in blood pressure.

A further point in interpreting autonomic effects is that the change in blood pressure produced by it may itself have unexpected indirect results. An example occurred in some recent work on a new non-inflammable anaesthetic, fluothane, which produces a profound fall in blood pressure largely by depressing central autonomic activity. The anaesthetic itself has practically no action on the neuromuscular junction. But if *d*-tubocurarine is given in its presence its action is somewhat intensified and, much more striking, enormously prolonged; neuromuscular transmission recovers very slowly; but if the fluothane inhalation ceases, then, as the blood pressure

begins to rise, recovery of transmission accelerates. Exactly the same thing can be seen with a ganglion blocking agent, where there may be no sign of recovery from quite a small dose of ganglion blocking agent until the hypotensive anaesthetic is withdrawn and the blood pressure begins to rise. One has to remember that one of the functions of the circulation is to distribute substances round the body; and since both hormones released in the body and injected drugs are the subject of continuous distribution and re-distribution, anything which lowers the blood pressure is likely to interfere with the normal time course and intensity of action of such agents. Examples such as I have quoted warn against too naïve an interpretation of the effects of autonomic paralysis.

THE RESULTS OF AUTONOMIC BLOCK ON NORMAL PHYSIOLOGY

The general picture of the sympathetic nervous system which emerged from the work of Cannon and his school was of an apparatus useful to the body principally in emergency states. But the first result I wish to mention, of the recent widespread use of ganglion blocking agents for investigation or treatment, has been to make plain that the sympathetic is very much concerned in everyday events. I would like to quote two illustrations. The postural hypotension after ganglion block is a cogent example. It shows not only that there are such things as postural vasomotor reflexes involved in everyday life (which was, indeed, known), but that they are quantitatively very substantial reflexes the removal of which, in the absence of some measure to prevent pooling of blood in the limbs and viscera, can be not only inconvenient but dangerous to the organism.

But the effects of inactivation of the sympathetic do not have as their principal effect only changes in blood pressure. Another effect of giving hexamethonium to a man is a fall in body temperature. Miss Steinberg and I observed it constantly in our practical class at University College in which the students received hexamethonium[7], and Dr. Morrison and her colleagues[2] saw it during an extended study of the effects of hexamethonium on limb blood flow and heat elimination. This loss of body temperature has a very simple cause, an increased loss of heat from vasodilated skin areas, particularly of the feet, but also of the lower part of the legs, sometimes of the hands, and probably also sometimes of the face. The fall in body temperature may be as much as 2° F. and may induce shivering. An

interesting paradox results, shivering in a subject with large areas of warm skin. Obviously the sympathetic is of major importance as a sort of sluice-gate for the calories in the body, controlling the rate of heat leakage to the outside world.

These two examples, together with much that Professor Barcroft said, make it certain that the sympathetic is involved to a really important degree in everyday life.

TYPES OF HYPOTENSION

A second change of viewpoint can be noted in the significance now attached to a hypertensive state. A firm distinction must be made between a fall in blood pressure produced by means such as a spinal anaesthesia, ganglion block or adrenaline antagonists (in which autonomic activity is reduced or paralysed), and falls in blood pressure produced by haemorrhage, histamine shock and other traumatic processes (in which the sympathetic is known to become very powerfully active). With autonomic paralysis, the blood volume is unaltered, capillary permeability is undamaged, and one may have fairly substantial falls in blood pressure without any notable reduction in blood flow to essential organs such as the brain, heart or kidneys. On the other hand, with hypotensions accompanied by shock, in which the circulating blood volume may be reduced either by leakage of plasma into the interstitial spaces or by frank loss of blood to the outside, one of the first actions of the body is to produce vasoconstriction, sometimes of the splanchnic area, of the skin, of the liver and kidney, possibly even of the heart and brain. In shocked states, therefore, a blood pressure comparable with that obtained by (say) ganglion block or spinal anaesthesia is accompanied by a far greater reduction of tissue blood flow. This seems likely to be the critical difference which leads in the shock-like states to the phenomenon often called 'irreversible shock', a phenomenon which has not yet been described for hypotensions produced by autonomic paralysis. The implications, of course, of this distinction between the hypotensive procedures are far-reaching; it is possible, for instance, that the autonomic reactions of the body to a reduced blood volume in shock may be harmful to the body. Certainly there is, in fact, evidence that autonomic block of some kind may confer protection against haemorrhage and other 'stressful' procedures. It is extraordinary that sustained hypotension produced by ganglion block or spinal anaesthesia is so well tolerated that a patient with a blood pressure of 70 mm. Hg may be fit for a

prolonged surgical operation. It is not fanciful to think that autonomic overactivity can be a serious liability to the body.

PATTERNS OF AUTONOMIC ACTIVITY

A last general point about the autonomic nervous system can also now be dealt with better in the light of new knowledge about ganglion block. It was at one time suggested that the two parts of the autonomic system, the sympathetic and the parasympathetic, might one or the other dominate the body in different individuals to different degrees. One might thus have in individuals in whom the sympathetic as a whole was overactive, or in whom the parasympathetic as a whole was overactive, a so-called 'sympatheticotonia' and 'parasympatheticotonia'. Now, if there was anything in this conception it should determine the pattern of response to a ganglion blocking agent; for, after such a drug, one should in the sympatheticotonic subjects see predominantly signs of sympathetic block; whereas in the parasympatheticotonic subjects (in which the sympathetic is *ex hypothesi* relatively inactive) the signs should be of parasympathetic block. Miss Steinberg and I, again in the practical class at University College, tested this by arranging that the students should make tests of nine different autonomic functions on volunteers among themselves; and we then examined the results to see whether the resulting block affected sympathetic functions as a whole or parasympathetic as a whole. We found, however, something quite different. The autonomic functions did not group themselves according to these two main heads; on the contrary, every individual out of some fifty or more whom we studied had a different pattern of autonomic reaction. It seemed indeed as though there was no single common pattern, but that every individual had his own type of activity, perhaps as characteristic of him as his physical constitution and his personality; one might even call it a sort of 'autonomic fingerprint'. This is a point which I think clinicians appreciate very well when controlling the blood pressure; it is generally recognized that every patient has to be titrated individually when receiving a ganglion blocking drug for hypertension. But it is perhaps not quite so well realized that the same variation in effect of ganglion block seems to extend to all the other autonomic functions which have been tested. It makes it clear that in a given individual the nervous factors controlling his circulation, although they may be using standard pathways common to us all, do in fact differ in pattern significantly and characteristically for each of us.

RESPONSE OF THE SYMPATHETIC NERVOUS SYSTEM TO INJURY

Ganglion block is not, of course, the only way of interfering with the autonomic outflow; and surgical interference has a long and honourable history. To review this would be impossible now. But I would like to finish with a brief account of some recent work by Murray and Thompson[6] in my laboratory, which is, I think, important for interpreting the results of sympathectomy, whether experimental or therapeutic.

They took up an old observation by Simeone, Cannon and Rosenblueth[9], that after a sympathetic ganglion had been partially denervated, a remarkably rapid return of function ensued. Murray and Thompson fully confirm this, finding, for instance, that after a 90 per cent denervation full function is restored in a few weeks. How could this return come about? One possibility is that the cut fibres regenerate: but the time required for function even to begin to return in this way is far longer, of the order of a hundred days or more, rather than a few weeks; and they verified that in fact regeneration had not taken place. A second possibility is that supersensitivity of the ganglion or smooth muscle develops, such that activity in a smaller number of sympathetic fibres can still lead to a nearly normal result. Now it is true that supersensitivity occurs in the early stages of recovery; but when function has fully returned to normal, it has disappeared again. The response to adrenaline and noradrenaline is not significantly different from normal; and the response to ganglion stimulants is likewise the same.

The explanation lies in a response not by the denervated structures, but by the normal intact fibres left behind. They emit fine axoplasmic shoots which enter and grow down the degenerating Schwann tubes left by the sectioned fibres. Thus they are guided to the ganglion cells deprived of a nerve-supply, and so restore innervation. The process can be readily seen histologically. It is a remarkably rapid process—obvious histologically within a few days of the denervation. It is a remarkably efficient one; 10 per cent of the original fibres can take the place, by collateral sprouting, of the missing 90 per cent, and even a 1 per cent residue can bring about a very substantial recovery. A fascinating result of such sprouting is that ganglion cells come to be innervated by preganglionic fibres with which they were not originally in contact. In the experiments just described the fibres from rami T4-7 (which normally cannot affect the pupil, which is normally innervated by T1-2 chiefly)

came to cause pupillary dilatation. In other words, recovery of function is accompanied by a re-routing of the autonomic pathways.

As an example of the implications of this work, consider the events after surgical sympathectomy. You will recall, in the detailed anatomy of sympathetic ganglionic tissue, that ganglion cells are met outside the main paravertebral ganglionic chain, on rami communicantes, and in the spinal nerves themselves (for references, see [1]). Now suppose by surgical means the chain is removed, we may readily find places where not only are autonomic pathways left intact, but where they lie in juxtaposition to pathways now undergoing degeneration. Clearly there is now a fertile field for sprouting, both pre- and post-ganglionically. It is not surprising that in some cases of sympathectomy for hypertension the blood-pressure returns disappointingly soon to its original high level. One can readily imagine a sprouting process underlying it. But there is a further point. Several observers have recorded, after sympathectomy, that not only may the blood pressure return to previous levels, but that (disconcertingly) the patient is as sensitive, or even more so, to ganglion blocking agents—and this in a patient supposedly deprived of his ganglia. Murray and Thompson found, however, in a study of the properties of the 'sprouted synapse', if one may call it so, that it is not completely normal; less acetylcholine than usual is released at the 'sprout' endings: and correspondingly the synapse is more sensitive to ganglion block. Thus the possibility of collateral sprouting in autonomic nerves offers an elegant explanation for a remarkable and otherwise rather puzzling result of cardiovascular surgery.

CONCLUSION

From such an outline, based on knowledge resulting from or stimulated by the development of specific drugs paralysing the autonomic control of the circulation, the sympathetic nervous system presents itself to us, I think, in a light somewhat different from the classical picture. It is in constant, important, everyday use, and is not simply an emergency system. Its stimulation may be harmful. Its pattern of activity is highly variable, probably specific to the individual. Finally, if damaged, it has a vigorous restorative power, that of collateral sprouting, which makes one view it less as a signalling system of relay stations and connecting cables, and more as a living and responsive tissue.

One cannot know whether Harvey, living today, would have

worked in this field. But, if we can accept that his blood pressure was raised, and that (anticipating the rice diet by 300 years) he put sugar in his salt cellars, I think we could count at least on his sympathetic interest.

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